Therapeutic Potential of *Nelumbo nucifera* (Sacred Lotus) in CNS Disorders

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(Received: September 24, 2021; Accepted: February 24, 2022; Published (Web): May 25, 2022)

ABSTRACT: *Nelumbo nucifera* (sacred lotus), locally known as Poddo, has been used as food and traditional remedy in Ayurvedic system in India and Traditional Chinese Medicine for a wide range of diseases. During past two decades, there are numerous scientific studies and general reviews have been published on its phytochemistry and pharmacology. However, in this paper, we aim to make a survey on neuropharmacological effects, as well as psychoactivities, of *N. nucifera*, identifying the active constituents and their proposed mechanism of actions which has not been systematically documented in the literature. Several online databases, including Google Scholar, PubMed, Web of Science, Science Direct, and Scopus were employed to conduct this survey. Previous studies have demonstrated that *N. nucifera* has potential neuropharmacological effects in various test systems, including *in vivo* animal models and *in vitro* cultured cells or enzymes through various mechanistic pathways, including 5-HT2_A receptor blockade, GABAergic system, regulating the NCAM and GAP-43 expression levels, regulating for skolin-stimulated cAMP production, and many more. Our survey showed that many alkaloids isolated from *N. nucifera* demonstrated antidepressant, sedative-hypnotic, anxiolytic, analgesia-potentiating action, anticonvulsant, antipsychotic, and memory enhancer activities. Although many studies have showed potential neurotherapeutic benefits of this plant and many of its constituents, but the focus of research towards clinical trial in human is rather very limited.

Key words: *Nelumbo nucifera*, lotus, Poddo, alkaloids, benzyl tetrahydroisoquinoline, flavonoids, neurological disorders

INTRODUCTION

Neurological disorder mainly affect brain and the spinal cord whereas, neurodegenerative diseases caused by nervous system cell death. Other CNS problem involved mental and physical disturbances termed as neurosis and on the other hand personality disorder caused by mental and emotional disturbances called phychosis. Among all of these CNS problems, neurological disorders and neurode-generative diseases remain as urgent unresolved medical challenge due to the lack of effective treatments.Among common CNS disorders, namely insomnia, anxiety, chronic pain anddepression, as well as Parkinson's and Alzheimer's diseases frequently cause noteworthy and life-threatening disabilities. The living standard of human is generally compromised by these conditions, which increases the risk of other long term mental illness. While currently accessible drugs can accomplish satisfactory symptomatic relief, serious side effects such as post traumatic amnesia, ataxia and cognitive disability, as well as risk of drug resistance, withdrawal symptoms followed by dependence and potential drug abusesome time restrict their clinical use.[1]

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Dhaka Univ. J. Pharm. Sci. **20**(3): 347-358, 2021 (June) Centennial Special Issue
DOI: https://doi.org/10.3329/dujps.v20i3.59800

Treatment with psychotropic drugs for an extended period may lead to numerous undesirable side effects, such as tiredness and addiction, or dire health consequences. As a result, in spite of having only mild effects on the central nervous system (CNS), many medicinal plants are more frequently being attempted to treat a variety of CNS disorders such as anxiety, pain, epilepsy, hysteria, convulsions, nightmares, etc. due to their traditional use and low toxicity. In the treatment of neurological disorders, natural products (NP) and herbal medications contains various chemical constituents which regulates the activity of different neurotransmitter systems, notably serotonin (5-HT), γ-aminobutyric acid (GABA), dopamine (DA), epinephrineand many more.[2,3]On the other hand, most of the antipsychotic NP's exhibit affinities for G-protein coupled receptors including the 5-HT2A serotonin and D2 dopamine receptors[2], as well as opioids and cannabinoid receptors. Up until now, two lotus species, *Nelumbo nucifera* and *Nymphaea caerulea*, have been used for their therapeutic potential towards neurological disorders.[4]

N. nucifera Gaertn. (Nymphaeaceae), an aquatic plant known as Poddo (in Bangla) (Figure 1), sacred lotus, Chinese water lily or water lotus, is extensively distributed throughout South-East Asia, including Bangladesh and have been used in traditional medicines (Table 1). In many south Asian countries various parts of this aquatic plant have been reported to have a wide array of traditional, medicinal and therapeutic uses.[5-8] In Eastern herbal medicine, the lotus is primarily known for calming emotional disturbances.[9] In Chinese traditional medicine (TCM), the *N. nucifera* flower plumule is utilized to treat nervous and sleep disorders, as well as high fever and restlessness[6,10], whereas the rhizome is used to improve neurological well-being and calmness.[11] Nevertheless, *N. nucifera* has been conventionally used to treat various CNS disorders such as pain, stress, anxiety, depression, etc.[12] The extract of *N. nucifera* also reported activity against neurodegenerative diseases.[13] Various benzyl tetrahydroisoquinolne (BTIQ) and aporphine (i.e., nuciferine and nornuciferine), alkaloids found in lotus flower and leaves[14] displayed many neuropharmacological activities. The alkaloid fraction of lotus leaveshave also showed prominent anxiolytic, sedative and hypnotic potential by binding with GABA receptor and stimulating the monoaminergic receptor system.[15]

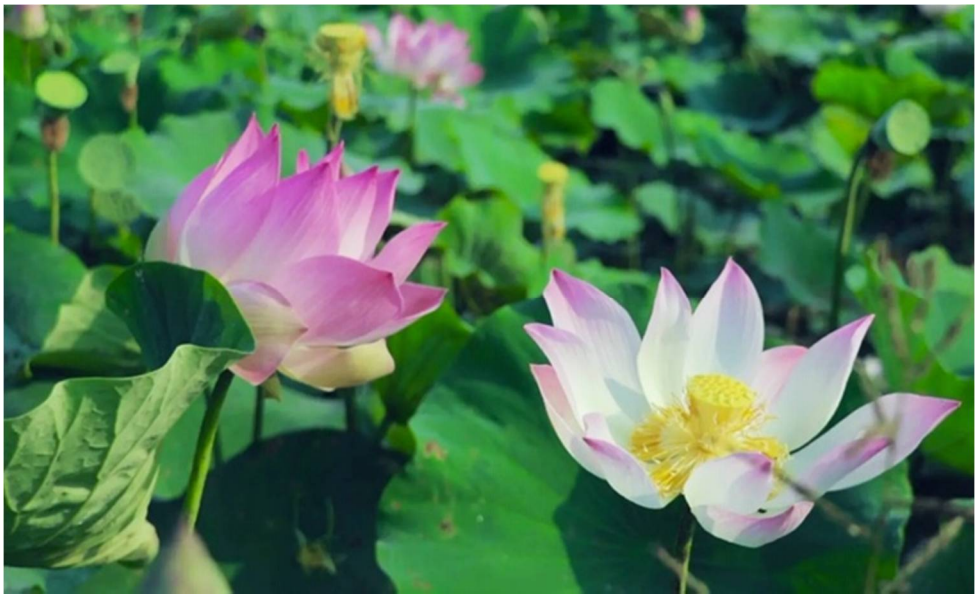

Figure 1. Image of *N. nucifera* flower and other parts (photo taken in Jashore, Bangladesh, on October 2020 by Abdur Rahman).

Several previous studied have demonstrated that neuroleptic drugs exert their function by blocking brain dopamine receptors.[16] In Ayurveda (traditional Indian medicine; TIM), nuciferine has been reported to be used in treating several clinical conditions including CNS disorders.[17] It is thought that nuciferine, which is an aporphine alkaloid, is responsible for the psychotropic effects of *N. nucifera* and *N. caerulea*.[18] Although chlorpromazine and nuciferine do not have similar chemical structures, nuciferine has been shown to exert chlorpromazine-like pharmacological activity.[19] In eastern medication, therapeutic effects of the lotus led to assume that nuciferine has a therapeutic profile similar to antipsychotics.[20] *In silico* predictions of all phytochemicals recognized in *N. nucifera* propose that nuciferine and its metabolites with various protein targets can cross the blood-brain barrier.[21] These assumptions and aforementioned information recommend that psychotropic impacts of nuciferine are due to its rich multi-pharmacological effect.[18]

The alkaloidal and non-alkaloidal compounds of *N. nucifera*, as well as its extracts, have been examined against various CNS disorders, for example, Alzheimer's disease (AD), Parkinson's disease (PD), anxiety, depression, schizophrenia and amnesia, which tabulated systematically in this report. Beside BTIQ alkaloids, other metabolites such as flavonoids, namely kaempferol, myricetin, quercetin, apigenin and luteolin showed significant neuroprotective effect which have also been reviewed in this report.

The aim of this review is to summarize the current literature evidence supporting the neuropharmacological effects of the plant *N. nucifera* (Sacred Lotus) that used traditionally for the treatment/management of some CNS disorders, as well as the underlying proposed mechanisms of action by compiling both *in vitro* and *in vivo* studies.

MATERIALS AND METHODS

Search strategy. On 20th December, 2020, an interdisciplinary search was conducted. A complete literature survey on *N. nucifera* was conducted by PubMed, Scopus, Google Scholar, Web of Sciences and ScienceDirect databases, using keywords "*N. nucifera*" and alkaloid, flavonoid, 'nuciferine', 'neuropharmacology', 'depression', 'psychopharmacology', 'behavioral study' and 'sedatives' were used. In this review, the following surveys were conducted, including (a) *in vivo*, *in vitro* and clinical studies of pure compounds from *N. nucifera* and extracts for liver diseases associated with neurology, (b) studies concerning mechanism of action (MoA) associated with the neuroprotective activity of extracts and/or constituents and (c) studies concerning the concentrations, doses and route of administration of extracts and its compounds.

Data extraction. The database searches for neuropharmacological activity of *N. nucifera* revealed 3370 records, of which 21 studies met the inclusion criteria. 3349 documents were excluded due to neither the title nor the abstract mentioning *N. nucifera*, duplication of information, and irrelevance of the study. The reports were screened for information according to the surname of the author, date of publication, alkaloid, flavonoid, test systems, observations, results, concentrations tested and suggested molecular mechanisms involved in the study.

RESULTS AND DISCUSSION

In traditional medicine, different plant parts of *N. nucifera*, such as leaves, seeds, flowers, and rhizomes, are used to treat various neurological disorders and diseases (Table 1). The therapeutic potential of these plant parts and the isolated compounds from the extracts (Figure 2) exhibited through various *in vitro* and *in vivo* test models (Table 2 and Table 3). BTIQ class of alkaloids (aporphine type) and flavonoids (flavanone, flavon, and flavonol type) are found to be the most active against various neuropharmacological disorders, including as sedatives, anticonvulsants, antidepressants and neuroprotective agents.[22,23] In addition, the pharmacokinetic parameters of the active aporphine alkaloids have also been studied.[24,25] Here we reporting some key neuropharmacological observations of *N. nucifera* extracts and its isolated compounds.

Table 1. Traditional uses of *N. nucifea.*

Scientific name	Family	Secondary metabolites	Plant parts	Traditional uses	Ref.
N. nucifera	Nymphaeaceae	Neferine, Nuciferine, Liensinine, (*s*)-armepavine, Isoliensinine, Asimilobine, Kaempferol, Pronuciferine	Leaves	Anti-inflammatory, antidiarrheal, anti-leprosy, anti-hemorrhoids, lipolytic, anti-obesity, cardiovascular and hypo-cholesterolaemic, analgesic, anthelmintic, anti-obese, hypolipidemic and antioxidant	26,55-59
			Rhizome	Diuretic, anti-psychopharmacological, anti-diabetic, anti-obesity, hypo-glycemic, antipyretic, anti-diarrheal, anti-skin infection and antioxidant.	
			Fruits and Seeds	Anti-hypertensive, diuretic, refrigerant, curing skin diseases, leprosy, and antidote	
			Flower	Anti-hyperglycemic, antipsychotic, anti-cholera, antipyretic, anti-diarrheal, and hepatoprotective, eye infections	

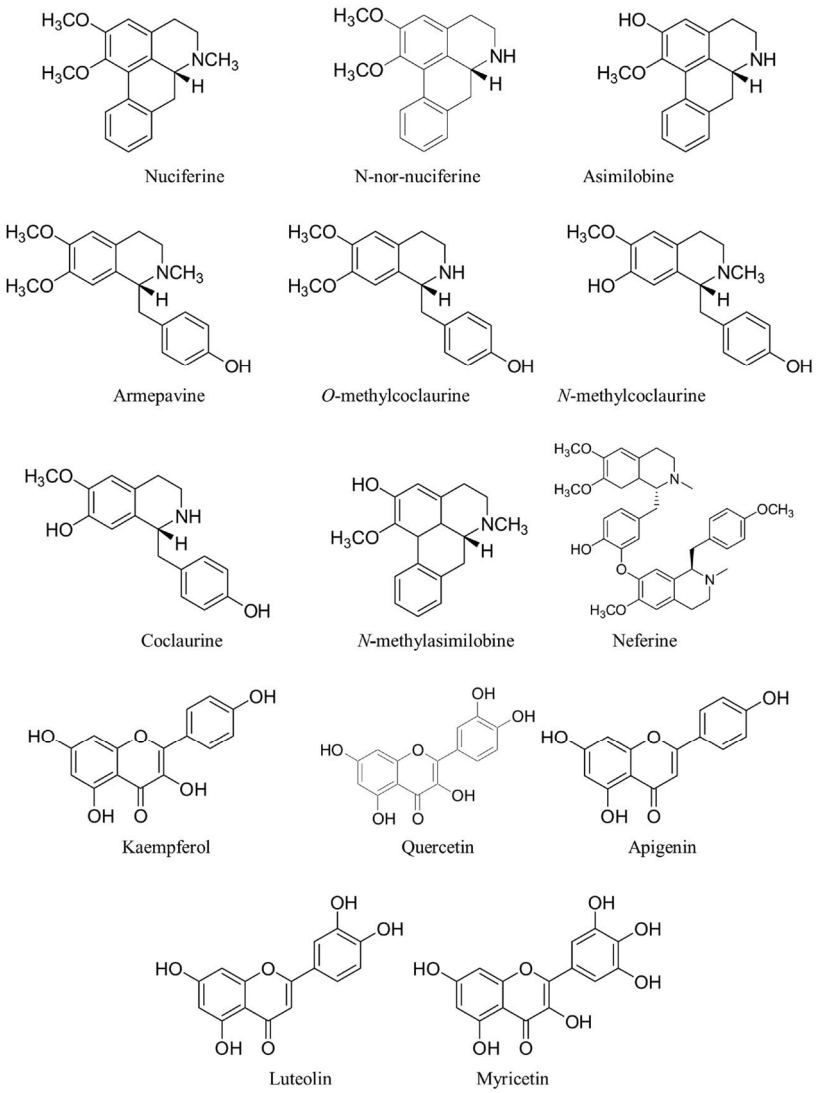

Figure 2. Chemical structures of compounds isolated from *N. nucifera*.

Table 2. Neuropharmacological activity of *N. nucifera* extract.

Test Model	Extract and Dose	Route of administration	Mechanism of action	Ref.
Locomotor activity study in *Drosophila* flies	Aqueous seed extract at 1, 5, 10 and 20 mg/ml	Oral	The sleep-promoting effect was due to the increase GAB_A and tryptophan activity in brain	53
Head-twitch response, pre-pulse inhibition and hyper locomotor activity in male Swiss mice	Nuciferine at 1.0, 3.0, or 10 mg/kg	Intraperitoneal (IP)	In rodent models nuciferine blocked head-twitch responses and discriminative stimulus effects of a 5-HT2A agonist,, enhanced amphetamine induced locomotor activity, inhibited phencyclidine (PCP)-induced locomotor activity, and rescued PCP-induced disruption of prepulse inhibition without induction of catalepsy.	18
Sedative-hypnotic and anxiolytic study in male mice	Alkaloidal extract of leaves at 20 and 40 mg/kg	Oral	The sedative-hypnotic and anxiolytic effect of the total alkaloid extract was due to the binding with $GABA_A$ receptors and activating the monoaminergic system.	15
Depression behavior activity study in chronic unpredictable mild stress (CUMS) male mice	Aqueous extract of stem at 200 and 400 mg/kg	Intragastrically (IG)	Anti-depression activity of the aqueous extract through the enhancement of neural cell-adhesion molecule (NCAM) and growth-associated protein-43 (GAP-43) expression levels in hippocampal neurons.	28
Neuropharmacological study in Swiss albino mice	Ethanolic extract of seeds at 50, 100 and 200 mg/kg	Orally	The ethanolic extract can act as nootropic agent having antistress activity by inhibition of noradrenaline function, interfere with serotonergic transmission as well as facilitation of some inhibitory systems like the GABA-ergic	32
Cannabinoid and opioid receptor radioligand binding assay in HEK293 cells	Chloroform fraction of flower at 10 µg/ml	*In-vitro*	Basic $CHCl_3$ fraction showed displacement activity of κ and µ receptors whereas acidic $CHCl_3$ fraction showed towards δ- and µ- receptors perhaps by disrupting membrane stability or changing the receptor conformation but showed no affinity for CB1 and CB2 receptors.	34
Behavioral study in Swiss mice	Chloroform fraction of flower 75-100 mg/kg	IP	*In-vivo*cannabimimetic-type effect observed for the acidic $CHCl_3$ fraction and the CNS activity of basic $CHCl_3$ fraction is likely mediated by other mechanisms since they did not show affinity for the in vitro CB1 or CB2 receptors	34
Locomotor activity study in *Drosophila* flies basal and caffeine-induced arousal conditions	Aqueous extract of seeds 0.25, 0.5, 1.0 mg/100 ml	Oral	The sleep-promoting effect was due to up-regulation of $GABA_A$/$GABA_B$ and serotonin receptors.	26
Psychopharmacological study in mice and rats	Methanolic extract of rhizome at 200, 300 and 400 mg/kg	IP	The extract decreased in exploratory behavioral pattern, reduced in muscle relaxant activity in rats and increased the pentobarbitone induced sleeping time in mice behaviour pattern as CNS depressant.	23
Spatial memory and hippocampal damage in stressed Wistar rat	Hydroalcoholic extract of flower at 10, 100 and 200 mg/kg	Oral	The protective effect of the extract against stress-related brain damage and dysfunction through improved oxidative stress, adult neurogenesis, and cholinergic and monoaminergic functions	36
Anti-Alzheimer's activities study via inhibitory assays of acetylcholinesterase (AChE), butyrylcholinesterase (BChE), and β-site amyloid precursor protein-cleaving enzyme 1 (BACE1)	Aqueous extract of leaves, de-embryo seeds, rhizomes, and stamens at 300 µg/ml	*In-vitro*	Antagonize all the enzymes BACE1, AChE, and BChE tested	60
Haloperidol-induced catalepsy rat model	Methanolic extract of seeds at 200-400 mg/kg	Oral	The extract restored the levels of thiobarbituric acid reactive substances (TBARS), Catalase and superoxide dismutase (SOD) levels in haloperidol induced catalepsy in rats.	40

Table 3. Effect of isolated phytoconstituents from *N. nucifera* in different neurological disorders.

Molecules	Experiments	Dose (Route)	Mechanisms	Ref.
Neferine	AChE, BChE, and BACE1 enzyme inhibitory assays	100 µM	Antagonize all the enzymes BACE1, AChE, and BChE tested	60
	$AlCl_3$ -induced Alzheimer's disease (AD) in rats	50 mg/kg (Oral)	Inhibit ROS formation, enhance antioxidant enzyme activity, declined the activity of acetylcholine esterase and Na^+-K^+ ATPase as well as inhibit neuroinflammatory cytokines expressions	61
	Neuroprotective effect in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced progressive Parkinson's mouse model	20 mg/kg (IP)	The protecting effect of Neferine from MPTP-induced Parkinsonism via acta as anti-inflammatory agent, decreased the levels of pro-inflammatory cytokines as well as increased the dopamine levels in substantianigra	62
	Anti-amnesic activities in scopolamine-induced amnesia mice models	10 mg/kg (oral)	Anti-amnesic effect of neferine mediated via antioxidant and anti-inflammatory capacities, as well as inhibition of ChEs and BACE1	63
Armepavin, O-methylcoclaurine, and coclaurine and neferine	Cannabinoid and opioid receptor binding affinities *in vitro*	10 µM	*In-vivo*cannabimimetic-type effect observed mediated with opioid δ, κ, and µ receptors binding	34
Coclaurine and nuciferine	Behavioral study in Swiss mice	10-100 mg/kg (IP)	Induced hypomotility, catalepsy, hypothermia, and analgesia activities mediated by cannabimimetic action	34
Nuciferine	Psychological study in rats	25-50 mg/kg (IP)	The CNS activity of nuciferine was confirmed due to its chlorpromazine-like neuroleptic activity	20
	Head-twitch response, locomotor activity, and catalepsy studies in mice	3-10 mg/kg (IP)	Antipsychotic activity of nuciferine by blocking head-twitch responses, as discriminative stimulus effects of a 5-HT2A agonist, substituted for clozapine discriminative stimulus, enhanced amphetamine induced locomotor activity.	17
Asimilobine and lirinidine	Serotonin induced contraction in rabbit isolated aorta	NA	Both alkaloids inhibited the contraction of rabbit isolated aorta through serotonergic receptor antagonist activity	64

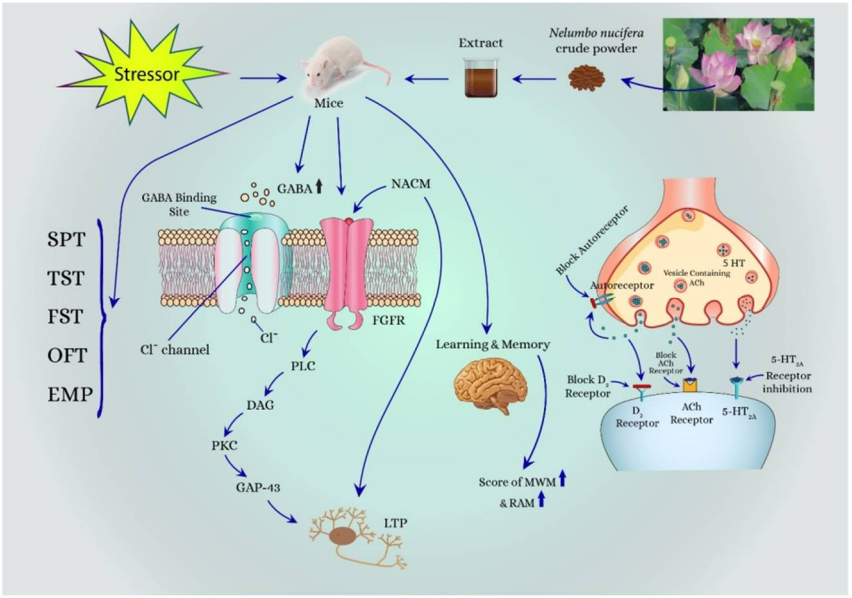

Figure 3. Proposed mechanisms of action of *N. nucifera* extract. Here, SPT: sucrose preference test; OFT: open field test; FST: forced swim test; EMP: elevated maze plus test; TST: tail suspension test; GABA: gamaaminobutyric acid; PLC: phosphokinase C; DAG: diacylglycerol, PKC: protein kinase C; GAP-43: growt associated proterin-43; LTP: long term potentiation; FGFR: fibroblast gowth factor receptor; 5-HT: 5-hydroxytryptomine; MWM:morries water maze; RAM: radial arm maze.

Effect on locomotor activity. Kyungae *et al.* (2018) reported that 0.1% caffeine and *N. nucifera* seed extractsappears to be significantly affect nocturnal activity, individual sleep botus number and total nocturnal sleep of Drosophila melanogaster.[26] Additionally, *N. nucifera* extract also had sleep-promoting potential even in drosophila with caffeine-induced wakefulness by enhancing total nighttime sleep duration, and suppressing nighttime activity and sleep episode numbers. Lotus seed extracts resulted in decreased locomotor activity and increased nocturnal sleep in both fruit flies and mice.[26] The molecular mechanism underlying these traditional sleep-remedies is that the alkaloids in the lotus extract bind to the $GABA_A$ receptor which increases the level of GABA in the brain and, consequently, causes a sedative-hypnotic effect.[27]

Additionally, nuciferine had conflicting activity on PCP and amphetamine-induced hyperlocomotion. Nuciferine reduced PCP-induced hyperlocomotion, subsequently causing recovery from PCP-induced disruption of pre-pulse inhibition without showing antagonism at the NMDA PCP binding site. In the case of amphetamine-induced hyperlocomotion, however, nuciferine caused higher motor activity.[18]Though a single dose of nuciferineshowed significant suppression of locomotor activity, multiple doses bring on drug tolerance and have a significant increase in locomotor activity.[15]

Effects on 2,5-dimethoxy-4-iodoamphetamine (DOI) -induced head-twitch response (HTR). Nuciferine has a time-dependent suppressive effect on 2,5-dimethoxy-4-iodoamphetamine (DOI)-induced head twitch response which is related to 5-HT2A antagonism. This head twitch response inhibition is most pronounced if nuciferine is pretreated 15 minutes before DOI.[18]

Anxiolytic effects. Both Zhao *et al.* (2020), and Rajput and Khan (2017) have reported *N. nucifera* extract as a strong anxiolytic agent owing to a highly significant time spent in open arms and number of open arm entries during elevated plus-maze (EPM) test.[28,29] Contrarily, Sugimoto *et al.* (2008) have reported that nuciferine shows antianxiety potential without muscle relaxant effects.[30] Yan MZ *et al.* (2015) suggested that anxiolytic effects are exhibited at a lower dose as a higher dose, its potential reduces this anxiolytic effect.[15] Flavones of lotus extract bind to the benzodiazepine site on the $GABA_A$ receptor and as a result, exhibited a highly significant anxiolytic effect.[31] Besides flavones, alkaloids, saponins, terpenes, terpenoids constituting the extract also acted as anxiolytic agents by synergistic action.[29,32]

Effects on depression. Better memory and greater learning ability are observed with higher residency time in the correct feeding arm and higher platform area crossing time, exhibiting the antidepressant potential of the lotus extract. This effect is further confirmed by high sucrose preference, increased latency to immobility, and decreased immobility time in the Forced-Swimming test. Lower immobility time in Tail-Suspension test is linked to serotonergic neurotransmission.[33]

In the Open Field test and Elevated PlusMaze test, the duration, distance, and entries in the center and open arm demonstrate the depression-suppressing effect of *N. nucifera* extract. Zhao *et al.* (2020) also suggested that the extract alleviates depression-like behavior by increasing neural cell-adhesion molecule (NCAM) and growth-associated protein-43 (GAP-43) expression.[28] In the zero-Maze test, *N. nucifera* ethanolic extract improved memory and learning ability by attenuating neurotransmission while nootropic activity is linked to the serotonergic transmission where nootropics suppress noradrenalin function.[32] The rhizome extract also displayed a muscle relaxant function.[23]

Effects on behavior. Though *in vivo* CB1 or CB2 receptors are unaffected, decreased locomotion, hypothermia, mild cannabimimetic type activity, ptosis, diminished motility, grooming behavior, increased antinociception and catalepsy are demonstrated.[20,34] The locomotion suppressing activity of nuciferine is due to its neuroleptic, dopamine blocker, and acetylcholinesterase

antagonistic behavior.[20,35] On the other hand, three BTIQ alkaloids O-methylcoclaurine, N-methylcoclaurine, coclaurine have affinities for kappa-opioid receptor, and linoleic acid and palmitic acid (1:1) mixture display affinity for delta- opioid receptor. However, both delta- and mu-opioid receptors have affinities for Bis-BTIQ neferine.[34] Antidepressant activity of *N. nucifera* extract responds by spontaneous activity, touch, sound, pain, and produces coordination loss and muscle relaxant activity responsible for exploratory behavior inhibition.[23]

Effects on sleep. *N. nucifera* extracts influences sleep physiology by involving in the GABAergic/serotonergic action. GABA (causing melatonin synthesis), tryptophan (involving serotonin and melatonin synthesis), quinidine (inhibit microsomal enzyme) is recognized in the *N. nucifera* extract. These compounds not only cause sleep promotion but also increase phenobarbital-induced sleeping.[26] The extract also enhanced phenobarbitone-induced sleeping[20], and *N. nucifera* rhizome, seed and leaf alkaloid extracts inhibit GABA receptor which involves potentiating sodium phenobarbital-induced CNS depression.[15] The total alkaloidal extractof lotus also acts as an allosteric activator to stimulate Cl-channel opening by binding to the GABA site on the $GABA_A$ receptor. This suggests that total alkaloidal extract has strong sedative-hypnotic and anxiolytic potential which is further related to increasing monoaminergic neurotransmission.[15,26]

Effects on memory and learning. The flower extract of *N. nucifera* was found to be an excellent neuroprotective and cognitive enhancer against stress-related brain injury and memory loss. The better oxidative stress state, higher adult neurogenesis, and increased neurotransmitters that play a role in learning and memory such as acetylcholine, dopamine, and norepinephrine are all probable underlying mechanisms. They can also help with stress-induced memory loss by acting as a neuroprotectant and memory enhancer.[36] The proposed mechanisms of this effects of *N. nucifera* are given in Figure 3.

Major depressive and anxiety disorders. In the prefrontal cortex, KPF increased the AKT/-catenin cascade which had antidepressant properties mediated by its antioxidant and anti-inflammatory effects.[37] KPF inhibited the enzyme fatty acid amide hydrolase (FAAH), which regulates the duration of activity of the endocannabinoid molecule (eCB) system, which controls complex circuits involved in anxiety-like states. Furthermore, Wistar rats given an EPM protocol showed that animals given KPF (40 mg/kg) had a lower fear response as well as a lowered freezing response.[38]

Effect on neurodegenerative diseases (Parkinson's disease (PD) and Alzheimer's disease). Parkinson's disease (PD) is the most common age-related chronic neurodegenerative illness, impacting predominantly individuals above 65 years old and accounting for 1-2% of the global population.[39] The methanolic seed extract of *N. nucifera* reported to attenuate PD symptoms tested in haloperidol-induced catalepsy rat model via restoring the levels of thiobarbituric acid reactive substances (TBARS), catalase and superoxide dismutase (SOD) levels in haloperidol induced catalepsy in rats.[40] Kaempferol (KPF) was on the main phytoconstituent in *N. nucifera*.[41] Literature study showed that KPF was found to improve the abscess of nigrostriatal dopaminergic neurons, decrease the growth of interleukin (IL) 1, IL-6, and TNF, and reduce the concentration of monocyte chemotactic protein-1 (MCP-1), intercellular cell adhesion molecule-1 (ICAM-1), and cyclooxygenase-2(COX-2) in BALB mice in a latest *in vivo* study. The HMGB1/TLR4 inflammatory mechanism was found to be inhibited by KPF, ensuring the integrity of the BBB.[42] The NLRP3 inflammasome, which is made up of the NLRP3-PYCARD-CASP1 protein complex involved for inducing caspase-1 and mature IL-1, was inactivated by KPF at doses of 25, 50, and 100 mg. Excessive activation of this complex causes a variety of inflammatory illnesses associated with aging, including Parkinson's disease.[43] Other research has

used mouse models of PD stimulated by the KPF at doses of 25, 50, and 100 mg, and found that KPF accelerated motor coordination, enhanced endogenous antioxidants SOD and its metabolites, elevated prevalence of striatal dopamine, and glutathione peroxidase (GSH-PX), and lowered malondialdehyde levels.[44]

Alzheimer's disease (AD), like PD, is also a neurological illness, but it causes memory and cognitive functions to deteriorate over time.[45] Suppression of the enzyme acetylcholinesterase, whose role is the breakdown of ACh in cholinergic synapses, is one of the most often utilized therapeutic interventions for the management of AD.[46] It is reported that *N. nucifera* seed embryos extracts showed anti-Alzheimer activity through protection of the aggregation of amyloid β peptide induced damage on PC-12 cells.[47] Kaempferol is an active constituent of *N. nucifera* and reports showed that utilizing an enriched KPF diet of transgenic drosophila flies that generate the A-42 protein in varied concentrations such as 10, 20, 30, and 40 µM of kaempferol for 30 days, it was observed that KPF can improve cognitive performance by inhibiting acetylcholinesterase activity.[48] AD is also associated with oxidative stress induced cognitive deficit. It is reported that receiving an intraperitoneal injection of KPF (10 mg/kg) for 21 days can improve cognitive impairment, hippocampal antioxidants level, and elevated neuro-inflammation markers in ovariectomized (OVX) rat models of sporadic AD.[49]KFP also reported to inhibits the stimulation of inflammatory processes such as factor nuclear kappa B (NF-B), toll-like receptor 4 (TLR4), p38 mitogen-activated protein kinases (p38MAPK), and AKT, which suppress BV-2 microglia signaling pathways and neuroinflammatory damage.[50]

Pharmacokinetic studies. The pharmaco-kinetics of the two most important alkaloids, nuciferine and noenuciferine were studied via oral and IV administrations. After oral administration, both nuciferine and nornuciferine were absorbed into the body and attained the plasma concentration at T_{max} of 0.9 and 1.65 h, with C_{max} of 1.71 and 0.57 µg/ml and eliminated with $t_{1/2}$,λz, of 2.48 and 2.94 h from the body, respectively. This suggests, both the compounds, nuciferine and nornuciferine have low elimination half-life (i.e., $t_{1/2}$, λz, 2.09, and 3.84 h, respectively) and larger Vd, λz, (9.48 and 15.17 L/kg, respectively). In contrast, after IV dose, both nuciferine and nornuciferine with the highest unbound concentration level of 0.32 and 0.16 µg/ml at 0.89 and 1.22 h, respectively, which suggest quicker crossing the blood-brain barrier. [24]

The cloned human receptor subtypes D2R (Dopamine D2 receptor), D3R (Dopamine D3 receptor) and D4R (Dopamine D4 receptor) are significantly inhibited (>70%) by specific radioligand binding with Bromo-benzyl tetrahydroisoquinolne (Br-BTIQ) and aporphine according to their concentrations. The affinity order of Br-BTIQ was D4R ≫ D3R > D2R, while aporphine has a D2R > D4R > D3R tendency.[25]

CONCLUSION

This review was inspired by the historic traditional neuropharmacologial use and benefit of *N. nucifera* by Ayurveda and TCM, where seed embryos (or plumule) of lotus are used to overcome nervous disorder, restlessness, and insomnia[6,51] and arrow-root prepared from the rhizome, named “OCE FUN”, for enhancing the mental health and quieting the spirits.[52] In addition, several lotus products are currently available online through internet as memory enhancer, sleep disorder remedies and neuroprotector.[53,54] In this review, we have considered neuropharmacological research on *N. nucifera* over the past two decade. A number of studies were reported that *N. nucifera* possesses a prominent neuropharmacological effect on various test systems. The sedative-hypnotic activity is associated with regulating the GABAergic/ serotonergic neuromodulators by increasing GABA contents which further induce Cl-channel opening. The nootropic activity of *N. nucifera* for spatial learning and memory is mainly linked to the central cholinergic system. Similar mode of action is also observed in serotonergic transmission and slight

inhibitory effect on noradrenaline function by *N. nucifera*. However, lotus extract and its alkaloids do not have any affinity for the CB1 and / or CB2 receptors, but it shows decreased locomotion, and increased antinociception and hypothermia *via* non-cannabinoid mechanisms. Moreover, antidepressant effects involve regulation of NCAM and GAP-43 and serotonergic neurotransmission - particularly involving 5HT1A receptors.

The overall findings with relation to the advantages of chemical elements in neurological illnesses suggest that research on *N. nucifera* and its constituents are mainly *in vitro* and *in vivo* studies, and data-related to preclinical and/clinical trials remain very negligeable. Therefore, more clinical and pharmacokinetic investigation on *N. nucifera* will be needed for future use as a therapeutic agent. In summary, this review reveals that *N. nucifera* can be an important traditional medicine to treat different CNS disorders. Finally, *N. nucifera* (Poddo or lotus) grows wildly in ponds, lakes and rivers around all over Bangladesh, which has a big potential for commercial cultivation as a basic raw material for research and development of neuropharmaceutical drug(s) and/ dietary supplement(s).

AUTHOR CONTRIBUTIONS

KM accumulated the literature and systematically analyzed the data. KM, MAR, RR, SJU and IM drafted and revised the manuscript. MAR draw the figures. SJU, HMR and IM supervised the project and provided helpful comments and revisions. All authors read and approved the final version of the manuscript.

FUNDING

Not applicable.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this paper.

DATA AVAILABILITY

All relevant data within this manuscript are fully available without any restriction.

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